REMARKS

Applicants respectfully request reconsideration and allowance of all pending claims.

I. Status of the Claims

In this Amendment D, claim 34 has been amended in order to more particularly claim certain embodiments herein. Support for the amendment to claim 34 may be found, for example, in paragraph [0016] of the published application (U.S. 2007/0071672), as well as in pending claim 46.

Accordingly, claims 34, 37-49 and 51-53 remain pending.

II. Withdrawn Claims

It is noted that the present Office Action, as well as the final Office Action mailed June 5, 2009, indicate that claims 37-44 have been withdrawn from consideration by the Examiner "as being drawn to a non-elected invention/species." As discussed in Applicants' Amendment C dated September 8, 2009, Applicants submit that the Office's withdrawal of claims 37-44 is improper, and therefore further submit that these claims should remain pending and under examination herein.

While Applicants still contend that withdrawal of these claims is improper, for the sake of brevity, the arguments presented in Applicants' Amendment C will not be repeated here.

III. Allowable Subject Matter

Applicants acknowledge that claims 51-53 are allowed.

IV. Rejection of Claims under 35 U.S.C. § 102(b)

Claims 34 and 49 are again rejected under 35 U.S.C. § 102(b) as anticipated by Dyszlewski *et al.* (Molecular Imaging, January 2002, Vol. 1, pages 24-35, hereinafter referred to as "Dyszlewski").

For the reasons set forth in Applicants' Amendment C, Applicants again respectfully submit that there is a clear difference between the compounds disclosed by Dyszlewski and those encompassed by Applicants' claim 34. However, without commenting further on the

appropriateness of the Office's rejection, for the reasons set forth below, Applicants respectfully submit that claim 34, as well as claim 49 dependent thereon, are not anticipated by Dyszlewski.

Dyszlewski discloses metal complexes with 2-methoxyisobutyl isonitrile ligands, wherein the **carbon** atom is bonded to the metal atom. This is clearly illustrated by Dyszlewski at page 25, figure 1, second and fourth structures, as well as by the text in the Abbreviations section on page 24. In contrast, Applicants' claim 34 states, in relevant part, that "the **nitrogen atom of the isocyanide is complexed with M**." (Emphasis added). Accordingly, there is clearly a structural difference between Applicants' claimed compounds and those disclosed by Dyszlewski.

Inasmuch as Dyszlewski **fails to disclose each and every limitation** of claim 34, as well as claim 49 depending therefrom, Applicants submit that these claims are **not** anticipated by Dyszlewski. Applicants therefore respectfully request withdrawal of this rejection.

V. Rejection of Claims under 35 U.S.C. §112

Claims 34, 45 and 47-49 are rejected under 35 U.S.C. § 112, second paragraph, as failing to comply with the written description requirement and for being indefinite, and 35 U.S.C. § 112, first paragraph, as being non-enabled. For the following reasons, Applicants submit that these rejections are improper, and respectfully request reconsideration thereof.

A. Written Description Rejection

The Office has rejected claims 34, 45, and 47-49 as failing to comply with the written description requirement. Applicants respectfully submit that the Office has failed to show why the claims fail to comply with the written description requirement, as required by the MPEP. Per the MPEP, "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." (MPEP § 2163 I. A., citing In re Wertheim, 191 USPQ 90, 97 (CCPA 1976)). The MPEP gives guidance as to three specific scenarios in which the written description requirement may not be met in original claims. **First**, the claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. **Second**, the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-

recognized correlation or relationship between the structure of the invention and its function. **Third**, a lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. (MPEP § 2163 I. A.) MPEP § 2163.4 further **requires** that the Office have a reasonable basis to challenge the adequacy of the written description, stating "[t]he examiner has the initial burden of presenting by a **preponderance of evidence** why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." (MPEP § 2163.4, *citing* Wertheim, 541 F.2d at 263, 191 USPQ at 97. Emphasis added.)

For the following reasons, Applicants respectfully submit the Office has not shown by a preponderance of evidence that the written description requirement has not been met. **First**, each feature of Applicant's claimed invention is fully described in the specification. The Office contends that the application does not sufficiently describe the invention as it relates to the other definitions for X_1, X_2, and X_3 when only two of the variables are selected from the group consisting of CO, NH_3, aromatic heterocycles, thioethers, and isocyanides. Applicants submit that one of ordinary skill in the art would be aware of which ligands would be appropriate when only two of X_1, X_2, and X_3 are selected from the group consisting of CO, NH_3, aromatic heterocycles, thioethers, and isocyanides. Applicants explain in their specification that compounds of claim 34 have the required chemotoxic activity if "at least **two** of the ligands in a compound as shown in formula I have been exchanged by guanine or guanosine after 3 days at 37°C with guanine or guanosine being present in a slight excess over rhenium or technetium." (Applicants' specification, paragraph [0021], *emphasis added.*) **Two** of the ligands in Applicants' claimed compound must exchange with guanine or guanosine, thus the importance in defining those **two ligands** in the claims. As one of ordinary skill in the art would understand in reading Applicants' specification, the identity of the *third ligand* is not crucial, as long as **two** of the ligands exchange with guanine or guanosine under the conditions set forth in Applicants' specification. Furthermore, Applicants' specification discloses several specific examples wherein one of X_1, X_2, and X_3 is a different ligand (such as for examples complexes 3, 7, 14, and 18-21 of figure 16, in which the third ligand is H_2O or a halogen).

Second, Applicants' claimed invention is not described solely in terms of a method of its making coupled with its function; rather, the specification provides a detailed correlation between the structure of the invention and its function. For example, paragraph [0021] sets

forth the correlation between the ligands being able to exchange with guanine or guanosine under specified conditions and chemotoxic activity. Thus, Applicants give both a method of making their claimed compounds, as well as a correlation between the structure and its function.

Finally, the Office has failed to show that one skilled in the art would not be permitted to immediately envisage or recognize the product claimed from the disclosed process, in view of the fact that Applicants have described their claimed compounds, given specific examples, and provided a correlation between structure and activity. Moreover, the Office has not presented by a preponderance of evidence reasons why a person skilled in the art would not recognize from Applicants' disclosure a description of the invention defined by the claims.

In view of the foregoing, Applicants respectfully request withdrawal of the written description rejection.

B. Enablement Rejection

Claims 34, 45, and 47-49 are rejected under 35 U.S.C. § 112, first paragraph, because the Office contends the specification does not provide enablement (i) for the third variable of X_1, X_2, and X_3 when only two variables are described, and (ii) to a person skilled in the art to make and use the invention commensurate in scope with the claims (*i.e.*, a method of treating cancer). Applicants respectfully disagree.

i. Enablement for the third variable of X_1, X_2 and X_3

Applicants respectfully submit the specification enables one skilled in the art to make and use the invention commensurate in scope with the claims. As explained above, Applicants' specification fully teaches one of ordinary skill in the art how to make the claimed invention. Per MPEP § 2164.01(b), "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a **reasonable correlation** to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." (Citing, In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)). Applicants, in their Examples, give both general and specific methods for making compounds as claimed, with both monodentate and bidentate ligands. (See, e.g., paragraphs [0060]-[0064]).

When a lack of enablement rejection is based on missing information, the Office is required to specifically identify what information is missing and why one skilled in the art could

not supply the information without undue experimentation. (MPEP § 2164.04). In the present case, the Office contends that defining only two of the variables of X_1, X_2 and X_3 in claim 34 renders this claim non-enabled. (Office Action of September 18, 2009, page 7, point 9).

Applicants respectfully submit that the Office has not shown why one skilled in the art could not supply the information without undue experimentation. Applicants provide specific examples of compounds with X_1, X_2 and X_3, wherein two of the variables are selected from the group consisting of CO, NH_3, aromatic heterocycles, thioethers, and isocyanides, and the third variable is another ligand. (See, e.g., figure 16, compounds 3, 7, 14, and 18-21). Additionally, as previously noted, Applicants give both general and specific examples of synthesizing the claimed compounds. (See, e.g., paragraphs [0060]-[0064]). Applicants further give a test for determining if a compound has the claimed anticancer activity, as set forth in the specification at paragraph [0021].

Applicants note that the Office acknowledges that the level of skill in the art is high. (Office Action of September 18, 2009, page 8). However, the Office has offered no reason why one of ordinary skill in the art, having a high level of skill in the art, upon reading Applicants' specification, would not be able to identify a third suitable ligand without undue experimentation. Accordingly, Applicants respectfully submit that the Office has not met its burden for showing Applicants claimed compounds are not enabled.

ii. Enablement for the treatment of cancer

Claims 34, 45, and 47-49 are further rejected under 35 U.S.C. § 112, first paragraph, as not enabled with respect to Applicants' claimed method of treating cancer. In response thereto, it is to first be noted that, in providing guidance for enablement of uses, the MPEP states that "[i]f a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." (MPEP § 2164.01(b) *citing* In re Johnson, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); In re Hitchings, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965); In re Brana, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993)). The MPEP further states that "[i]f one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph." (MPEP § 2164.01(b).) Finally, it is to be noted that the MPEP further states that

"[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." (MPEP § 2164.01, *citing* In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)).

Applicants respectfully submit that the specification provides the necessary guidance for one skilled in the art to make and use the invention commensurate in scope with the pending claims, and thus fully meet the requirements for enablement. Specifically, Applicants submit that the Office, in analyzing the Wands factors, have not given significant weight to the teachings in Applicants' specification.

In the specification, Applicants specifically teach that the compounds disclosed and claimed therein have anticancer activity that is mechanistically similar to that of the well-known anticancer agent cisplatin. (See, *e.g.*, paragraphs [0007] and [0023]). In particular, Applicants point the Office's attention to the following explanatory paragraphs from their specification:

> [0007] It was found according to the invention that the $[M(CO)_3]^+$ core (M=Re, Tc) **can bind oligonucleotides comprising a GG motif with good stability and can cause similar structural changes in DNA as cisplatin**. This was unexpected because the skilled person would expect coordination of this core to DNA bases to result in sterically too crowded complexes to have good stability. It was furthermore found that the $[M(CO)_3]^+$ core **surrounded by a proper set of ligands is chemotoxic and when M is a radioactive isotope also radiotoxic.**
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> [0019] In a particular embodiment the bidentate ligand is an anionic amino acid. The advantage thereof is that amino acids are cleaved from the Re(I)- or Tc(I)-center at lower pH as encountered e.g. in cancer cells and lysosomes, thus, releasing the active part of the complex as a drug . . . While not wishing to be bound by theory, it is believed that since the two methyl groups are sterically demanding and the ligand is weaker bound to Re(I) or Tc(I) than [the ligand], this entails easier release at lower pH.
>
> [0023] The compounds herein described and used in accordance with the invention are based on mono-nuclear octahedral complexes of metal ions which combine the inherent radioactivity of the metal center with the **mechanistic properties of cisplatin.** This is unexpected since octahedral complexes are in general believed to be sterically too crowded to interact with DNA in a comparable way. **Despite that, the present inventors have demonstrated that two nucleo-purines bind the Re(I) center in cis arrangement and do so at a rate comparable to that of platinum compounds leading to a chemotoxic activity comparable to cisplatin.**

[0025] It is also shown by the present inventors that rhenium complexes with at least two available coordination sites influence the tertiary structure of ΦX174 DNA by altering the electrophoretic mobility of the open circular and the supercoiled form of plasmid DNA. The $[Re(I)(CO)_3]^+$ moiety **displays a principally similar reactivity pattern with plasmid DNA as *e.g.* cisplatin**. It binds selectively to two free guanines, implying a possible interaction with adjacent guanines in DNA as well. The induced changes involve covalent binding to two bases rather than simple electrostatic interaction.

[0027] The improvements of the above mentioned compounds over the current state of the art are the following. Mono-nuclear octahedral $^{186}Re(I)$ or $^{188}Re(I)$ complexes can combine the radioactivity of the metal center with the ability of intra-or interstrand linking in DNA. Such a class of compounds can inhibit DNA transcription while delivering a highly localized radiation dose in the target tumor tissues. This type of complex can thus act as chemotoxic radiopharmaceuticals suitable for cancer therapy. Mono-nuclear octahedral $^{99m}Tc(I)$ complexes can be used as diagnostic analogs of the above $^{186}Re(I)$ or $^{188}Re(I)$ compounds. (Emphasis added).

These are only some representative teachings from throughout Applicants' specification. Applicants also include specific tests for anticancer activity, such as outlined in paragraph [0021]. Paragraph [0028] teaches modifying the compounds with vectors, which allows targeting, active uptake and degradation in the cytoplasm. Example 3 shows binding of the compounds to guanine and Example 4 shows formation of a bis-guanine adduct using a compound as claimed. Example 5 shows interaction between claimed compounds and oligonucleotides. Example 6 shows interaction of claimed compounds with ΦX174 Plasmid DNA. Example 7 shows that 2 labile ligands, as required by Applicants' claims, are required to induce structural changes of ΦX174 Plasmid DNA. Example 9 shows the stability of the $[M(CO)_3]^+$ΦX174 Plasmid DNA Adducts. Example 10 sets forth a procedure for testing cytotoxicity, and Examples 11-14 show cytotoxicity of claimed complexes towards four different cell lines.

Moreover, this non-exhaustive list shows that Applicants, throughout their specification, provide one of skill in the art with considerable information for making and using the complexes described therein as anti-cancer agents, without having to engage in experimentation beyond what is typical. Specifically, Applicants show that their compounds work in a manner that is mechanistically similar to cisplatin; thus, they have provided guidance as to the predictability of the anticancer activity of these compounds.

In view of the foregoing, it is respectfully submitted that Applicants have provided extensive guidance throughout their specification as to selecting, synthesizing, and testing the

activity of the claimed compounds, all of which is within the typical scope of experimentation. In addition, Applicants specifically show activity against specific cancer cell lines. Thus, Applicants submit that claims 34, 45, and 47-49 are enabled by the specification, and respectfully request withdrawal of this rejection.

C. Indefiniteness Rejection

Claims 34, 45, and 47-49 are rejected under 35 U.S.C. § 112, second paragraph as indefinite. The Office contends that the claims, as written, are ambiguous because the phrase "at least two of X_1, X_2 and X_3 are monodentate ligands selected from the group consisting of CO, NH_3, aromatic heterocycles, thioethers, and isocyanides," identifies only two of three ligands, leaving the identity of the third ligand unclear. (Office Action of September 18, 2009, page 9-10, point 11).

The definiteness requirement of 35 U.S.C. § 112, second paragraph requires that the claims particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. The MPEP explains that the Office will "allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness." (MPEP § 2171). The MPEP further states that "[s]ome latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity." (MPEP § 2173.02).

Per MPEP § 2173.02, definiteness must be analyzed in light of (A) the content of the particular application disclosure; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Applicants respectfully submit that claim 34 meets this threshold requirement for definiteness.

The Office's specific issue with claim 34 appears to be that it only defines two of the variables X_1, X_2, and X_3. As explained above, Applicants' specification makes clear that compounds of claim 34 have the required chemotoxic activity if "at least **two** of the ligands in a compound as shown in formula I have been exchanged by guanine or guanosine after 3 days at 37°C with guanine or guanosine being present in a slight excess over rhenium or technetium." (See, e.g., paragraph [0021]. Emphasis added.) Thus, Applicants explain the importance in

defining **two of the ligands** in the claims. As one of ordinary skill in the art would understand in reading Applicants' specification, the identity of the *third ligand* is not critical, as long as **two** of the ligands exchange with guanine or guanosine under the conditions set forth in Applicants' specification. Furthermore, as described above, Applicants' specification discloses several specific examples wherein one of X_1, X_2, and X_3 is a different ligand (such as complexes 3, 7, 14, and 18-21 of figure 16, in which the third ligand is H_2O or a halogen).

For these reasons, Applicants respectfully submit that claim 34, and 45, and 47-49 dependent thereon, meet the statutory threshold for definiteness. Applicants therefore respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration and allowance of all pending claims.

Applicants do not believe that a fee is due in connection with the submission of this Amendment D. However, if the Office determines that a fee is due, Applicants hereby authorize the Commissioner to charge Deposit Account No. 13-1160.

Respectfully submitted,

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VIA EFS